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Secondary Malignancies in a Child With Hodgkin's Disease: Peripheral T-Cell Lymphoma and Myelodysplastic Syndrome Evolving Into Acute Nonlymphoblastic Leukaemia

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Hodgkin's disease (HD) has been linked to an increased risk of second malignant neoplasms (SMN), especially non-Hodgkin's lymphoma (NHL) and acute nonlymphoblastic leukaemia (ANLL). The mutagenic property of cytotoxic therapy as well as defective immunity have been implicated as playing a major role in the development of SMN in patients previously treated for HD. We report a case of a 14-year-old girl with HD who developed two different second malignancies within a latent period of 28 months following HD diagnosis. The patient presented initially with bilateral cervical and supraclavicular as well as mediastinal and paraaortic lymphadenopathy. She was staged as IIIA, nodular sclerosing type HD, and was given eight alternative cycles of MOPP-ABVD followed by "mantle" field radiotherapy to a total dose of 3.3 Gy plus 0.4 Gy to the upper mediastinum. Within 8 months following the completion of therapy, a period of myelodysplasia and progressive severe immune deficiency, considered as a result of initial treatment, occurred. Eighteen months after HD diagnosis while the patient was continuously neutropenic and heavily immunocompromised, a peripheral T-cell lymphoma of the angiocentric immunoproliferative lesion type (AIL) Grade III, appeared in both lungs within and beyond the radiation field, with no evidence of HD in biopsy specimens. After institution of a new chemotherapy regimen (L17M), a satisfactory response regarding NHL lesions was noted. However, 10 months later the myelodysplastic syndrome (MDS) accompanied by complex chromosomal abnormalities evoluted to frank ANLL with a rapid fatal course. This case supports the hypothesis that combined modality treatment accompanied by severe immunodeficiency may result in the development of multiple second malignancies even within a very short latent period, especially in a subgroup of HD patients who may be at particularly increased risk for second cancers.

Key words: Hodgkin's disease (HD), childhood, peripheral T-cell lymphoma, non-Hodgkin's lymphoma (NHL), acute nonlymphoblastic leukaemia (ANLL), second malignant neoplasms (SMN)

INTRODUCTION

During the last three decades, significant improvement has been achieved in the survival of children with Hodgkin's disease (HD). However, the applied treatment consisting either of chemotherapy combined with radiotherapy or radiotherapy alone may result in early toxicity and/or late complications [1]. The development of second malignant neoplasms (SMN) in these patients is the most serious late effect. The time from initial HD diagnosis to the appearance of SMN ranges from 2–10 or more years and varies according to the SMN type. It is noteworthy that acute nonlymphoblastic leukaemia (ANLL) and non-Hodgkin's lymphoma (NHL) are the most frequent early second malignancies [2,3], whereas solid tumors (e.g., sarcomas, thyroid cancer) may appear later [4].

Mechanisms underlying the pathogenesis of these second malignancies are being continuously elucidated. Mutagenic effects of cytotoxic therapy [5], histologic conversion of HD [6], and defective immune surveillance in patients previously treated for HD [7] have been considered as major causes of SMN.

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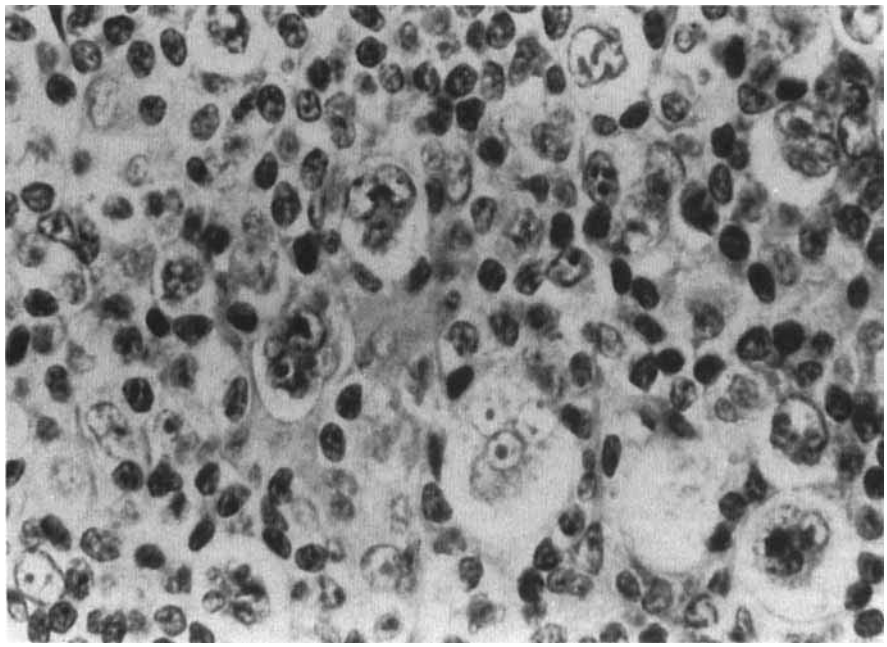

Fig. 1. Lymph node: Hodgkin's disease, nodular-sclerosing type (H and E×400).

We describe the case of a 14-year-old girl with HD who developed two different second malignancies: a peripheral T-cell lymphoma of the lungs of the AIL type, Grade III, and a myelodysplastic syndrome (MDS) with complex chromosomal abnormalities evoluting to ANLL within a short latent period of 28 months following HD diagnosis.

CASE REPORT

A 14-year-old girl was investigated for progressive painless enlargement of cervical and supraclavicular lymph nodes. There were no other accompanying symptoms. She and her family had no history of infectious mononucleosis or immunodeficiency. No lymphadenopathy in other regions or hepatosplenomegaly was found at physical examination. Investigation with CT scans plus pedal lymphangiography disclosed additionally: (1) an enlargement of upper mediastinal and right pulmonary hilar lymph nodes, (2) an anterior mediastinal tumor mass 5 cm in diameter, and (3) involvement of the paraaortic lymph nodes.

An excisional biopsy specimen of an enlarged cervical lymph node showed complete effacement of the normal lymph node architecture due to involvement of HD of the nodular sclerosing type (Fig. 1). Peripheral blood, bone marrow, and karyotype examination of bone marrow (BM) cells were normal. Serum immunoglobulin levels (Igs) and lymphocyte subsets were normal for the patient's age, and serologic detection of EBV, CMV, and HIV at diagnosis was negative.

According to the Ann Arbor classification, the patient was staged as III A clinical stage HD. Chemotherapy consisting of eight alternative cycles of ABVD-MOPP was instituted and accompanied by radiotherapy (RT) according to the "mantle technique" with 3.3 Gy plus 0.4 Gy to the upper mediastinum.

Three months after the completion of RT, the child presented with interstitial pneumonitis, which extended further than the mediastinal radiation therapy portal. Spirometry showed impaired respiratory function, but no specific pathologic findings were noticed during bronchoscopy (performed with a flexible bronchoscope) and in the examination of a bronchoalveolar lavage. Investigation for EBV, CMV, HSV_{1-2}, RSV, adenovirus, mucoplasma pneumoniae, and pneumocystis carinii was negative. Interstitial pneumonitis was attributed to the sequencing of bleomycin and RT. The patient completely recovered following therapy with prednizone, rifampicin, co-trimoxazole, and acyclovir, which were given empirically.

During the next 8 months while off treatment, the patient developed progressive anaemia, thrombocytopenia, and neutropenia resulting in complete peripheral blood cell aplasia. Bone marrow aspiration and biopsy showed myelodysplastic features of BM cells that were attributed to initial treatment. Parallel karyotypic analysis

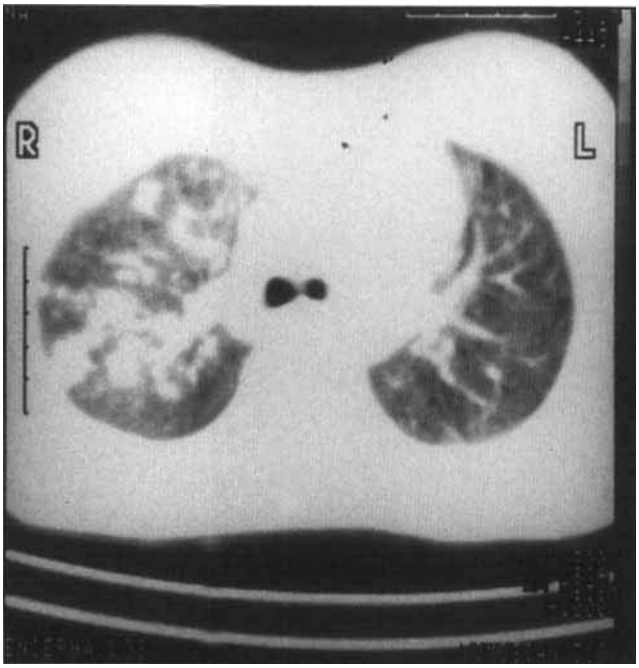

Fig. 2. Thorax CT scan showing multiple nodular lesions in both lungs.

of BM cells was normal (46XX) and reevaluation of HD at regular intervals showed the basic disease in complete remission.

In addition to the myelodysplasia, several progressive disorders of the patient's immune system were found: (1) a severe decrease in all immunoglobulins (mean values of IgG = 591.6 mg/dl IgA = 26.6 mg/dl IgM = 9.3 mg/dl, (2) a decline of B and T lymphocytes, (3) an inversion of the T4: T8 ratio (2.1 to 0.4), and (4) a significant increase in natural killer cells and monocytes. The patient's immunodeficiency continuously deteriorated, and she presented frequent systematic infections with gram (−) bacteria, which were managed with broad spectrum antibiotics.

The main therapeutic approach to her myelodysplasia and immunodeficiency, apart from supportive therapy (packed red cells and single donor platelet transfusions, irradiated, filtered, and CMV negative), was the use of combinations of recombinant haematopoietic growth factors (rhG-CSF, rhGM-CSF, rh-erythropoietin). However, the patient's haematological indices or immune status did not improve.

During a routine chest X-ray 18 months after the initial diagnosis, nodular lesions in both lungs were found and confirmed by a CT scan (Fig. 2). Thoracotomy followed, and the multiple lung biopsies taken from these nodular lesions demonstrated partial or complete effacement of the normal lung architecture due to an extensive neoplastic lymphoid proliferation with a characteristic angiocentric and angiodestructive growth pattern (Fig. 3).

On cytological grounds, the neoplastic infiltrate consisted of small, medium, and large lymphocytes with moderate to marked atypia. Immunophenotypically, the lymphocytes were almost exclusively of T cell origin: $CD_{45}(+)$, $CD_3(+)$, CD_{45} RO(+), CD_{20} ass (L26)(−) (Fig. 4). Histiocytes, low numbers of eosinophils, plasma cells, and prominent necrosis were part of the histological appearance of these lesions. Both small arteries and veins were involved; the vessels displayed mural infiltration by atypical lymphoid cells, which very often eroded and/or obliterated their wall and lumen. To summarize, the histological and immunohistological findings were compatible with angiocentric immunoproliferative lesion, Grade III, which according to Lipford et al. [8] represents a peripheral T-cell lymphoma (Fig. 5).

Investigations for EBV (virus capsid and nuclear antigen IgG-IgM), human T-cell leukaemia virus (HTLV-I), and HIV infection at the time of diagnosis of NHL were again negative.

Parallel to the NHL detection, a BM aspiration showed myelodysplasia progression accompanied by an increase of myeloblasts and monocytoblasts (up to 15–20% of the mononuclear cells). A new BM biopsy revealed bone marrow spaces with increased cellularity alternating with areas of bone marrow damage and increased reticulin fibers. The granulocytic series was characterised by a shift toward immature forms [40% lysozyme (+), CD68-KP1(+)] with some degree of maturation arrest. The erythroid series was hyperplastic with dyserythropoietic changes. The megakaryocytes were within normal range but a number of them had dysplastic features (Fig. 6). These histological findings in assessment with the clinical history of the patient were interpreted as secondary, therapy-related MDS (RAEB-t according to FAB classification). Cytogenetic analysis of BM cells now detected acquired clonal chromosome abnormalities: 46XXdel 1q (q32 → qter) in all metaphases plus another clone with 45XX-7del 1q (q32 → qter) defined in 30% of the examined metaphases.

After the diagnosis of NHL, chemotherapy was instituted according to the L-17M protocol [9], which included a combination of VCR, CTX, ADM, PDN, 6TG, ARAC, BiCNU, L-ASP, and DACT. This regimen resulted in a satisfactory response. However, 10 months later frank ANNL (M_4) evoluted with high numbers of circulating blast cells. A rapid deteriorating course followed and 28 months after the initial diagnosis of HD the patient died following sepsis and cardiopulmonary arrest.

DISCUSSION

The therapeutic approach comprising the combination of chemotherapy with radiotherapy (RT) on patients with

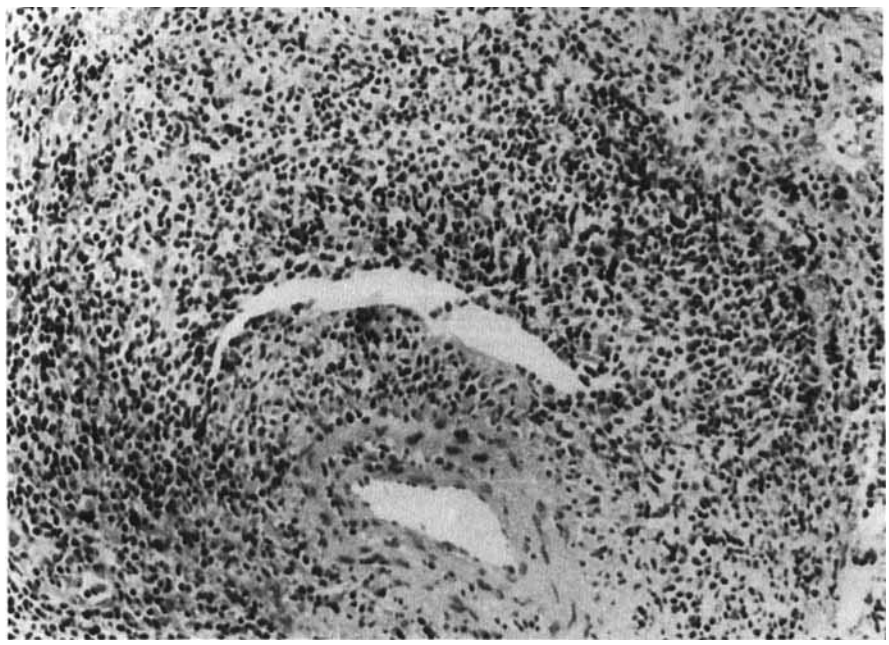

Fig. 3. Lung biopsy: Angiocentric and angiodestructive neoplastic lymphoid infiltration (H and E×100).

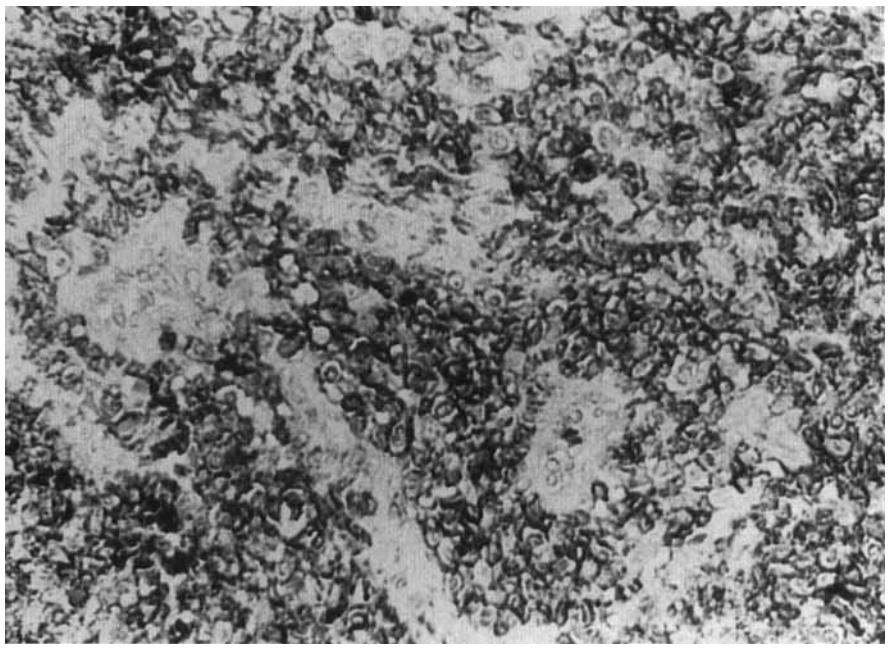

Fig. 4. Lung biopsy: Paraffin sections immunostained with the antibody CD3. The neoplastic lymphocytes are T lymphocytes as shown by their staining with CD3 (×200).

disseminated HD has led to a very satisfactory disease-free survival (DFS) in children. DFS even in the late stages of disease ranges between 60–70% [10]. However, late effects of chemotherapy and RT hinder this positive outcome. Children, as growing organisms, constitute the most susceptible population to these side effects [11].

The awareness that second cancers could be a complication of aggressive therapy arose first from the experience of the National Cancer Institute, in patients with extended disease [12] where chemotherapy sometimes combined with RT succeeded in achieving long-term survival. It was felt that second malignant neoplasms

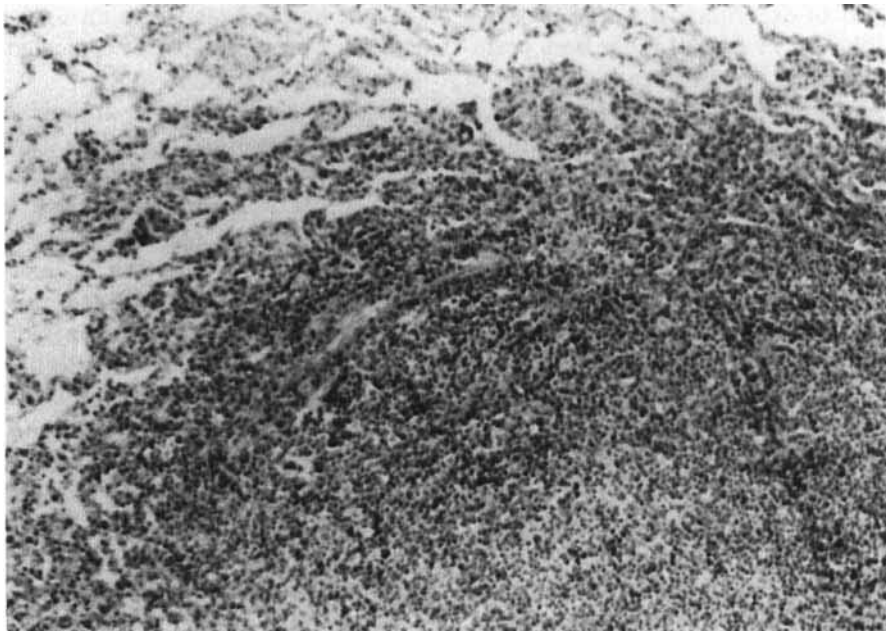

Fig. 5. Angiocentric immunoproliferative lesion (Grade III) of the lung. An angiocentric infiltrate of lymphoid cells is associated with parenchymal consolidation (H and E×100).

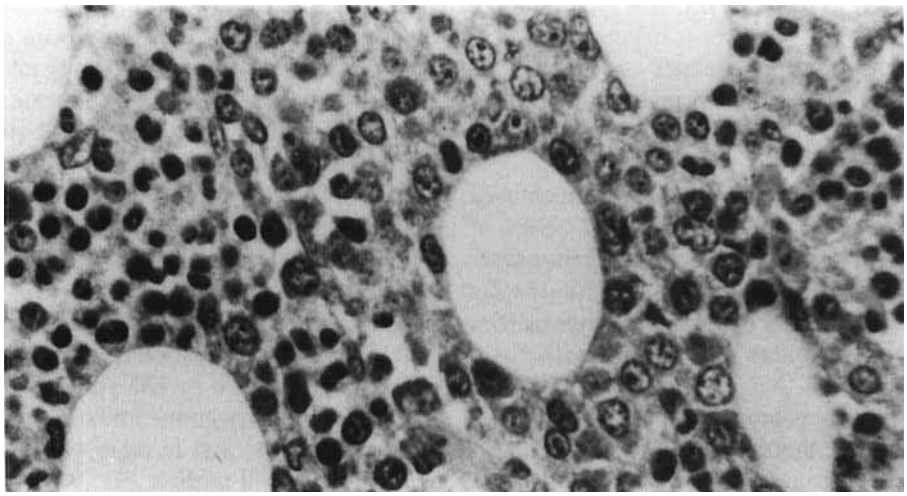

Fig. 6. Bone marrow biopsy: Shift to the left of the myeloid series and erythroid hyperplasia with dyserythropoiesis.

(SMN) were strongly associated with the sequencing of RT and chemotherapy [13]. Chemotherapy with alkylating agents in HD was also shown in cohort studies to increase the risk of secondary ANLL or NHL [14,15]. Our patient with a stage III A nodular sclerosing HD received aggressive therapy, which included alkylating agents (nitrogen mustard and procarbazine) and doxorubicin plus "mantle" field RT for a period of 8 months.

The interstitial pneumonitis noted 3 months after the completion of RT was the first treatment-related side effect. Bleomycin and "mantle" technique RT given in cumulated doses of 100 mg/sq.m and 3.3 Gy, respectively, were identified as the most probable etiologic factors. Such doses strongly predispose the patient to the development of interstitial pneumonitis [11] within a short latent period of 6–12 weeks.

In our case, following the end of treatment, a diagnosis of secondary MDS was established from peripheral blood and BM smears as well as from BM biopsy findings. A correlation between the intensity of prior therapy

given either to patients or experimental animals and the risk of developing either MDS or ANLL has been postulated [16]. Among all the chemotherapeutic inducers of MDS and ANLL, alkylating agents predominate. It has been well recognised that in >85% of patients who develop chemotherapy-induced ANLL, an alkylating agent has been used [17]. It also has been well documented that a myelodysplastic or preleukaemia phase is observed in at least 70% of patients who develop therapy-related ANLL [18]. It seems that when a longer follow-up is available, nearly all these patients probably experience a preleukaemia phase, as did our patient [16,17]. This contrasts with de novo ANLL, for which only 20% of patients have a similar prodromal syndrome [19]. The mean duration of the latent period between the MDS phase and overt ANLL has been reported to be up to 11.2 months, whereas the mean survival time after the diagnosis of ANLL ranges between 4 to 6 months [19].

The risk of the onset of leukaemia has been reported to be highest between 24 and 72 months after the initiation of either chemotherapy or RT with a steady decline in incidence thereafter. In patients who develop leukaemia, $\simeq 6\%$ have the onset within the first year following the initiation of mutagenic therapy [16]. In our patient, secondary MDS evoluted to overt ANLL-M4 type within a 12-month period.

Characteristic chromosome defects of BM cells emerged during the process of MDS, involving the chromosome 1 [del 1q (q32 qter)] and chromosome 7 (monosomy 7).

Referring to the chromosome abnormalities identified in such cases, Rowley et al. [20] observed that >90% of patients developing preleukaemia and leukaemia subsequent to treatment for lymphoma had a chromosomally abnormal clone. The most common abnormalities were either partial or complete loss of chromosomes 5 and/or 7 [20].

More specifically, monosomy 7 has been reported to be the sole chromosome abnormality in 50% of patients during the preleukaemia phase [21]. The appearance of monosomy 7 has been connected with high doses of alkylating agents comparable to those given to our patient [22,23].

Eighteen months after the HD diagnosis a peripheral T-cell NHL of the AIL type, Grade III of the lungs appeared with no evidence of residual HD in multiple lung biopsies.

Like acute leukaemia, NHL may represent another cancer that has a substantial risk of appearing after combined modality therapy [24]. In our case, the short interval of 18 months from HD diagnosis to the development of NHL is unusual. Nevertheless, secondary NHLs have in rare cases been reported to appear very early on, after the initial diagnosis in patients with HD [25]. In a report of Meadows et al. [25], an interval time of 0.8–9.5 years after the initial diagnosis to the appearance of NHL was noted in a large number of evaluated HD paediatric patients with a long follow-up.

The incidence of NHL following treatment of HD ranges between 0 and 5.9% [1]. It has been reported [1] that among 114 patients with HD who developed secondary NHL, in 28% the initial diagnosis was nodular lymphocyte predominance HD (NLPHD). This finding seems to be far from the incidence of 3.2% of this histologic subtype observed in the overall population of HD, as reviewed by the Lymphoma Pathology Pannel [26]. Therefore, the NLPHD seems to be the histologic subtype more often correlated with an increased probability of coexisting with and/or evoluting to NHL [27], usually of B-cell origin. The results of Timens and coworkers [28] indicated that NLPHD may be a germinal center lymphoma. According to the same authors, the transformation or evolution of NLPHD to NHL could be considered as a part of its natural history. However, this mechanism seems unlikely in explaining the development of the T-cell origin lymphoma in our patient with the nodular sclerosing type of HD.

There is no doubt that many other aetiopathogenetic mechanisms do exist, and the development of secondary NHL after HD may be multifactorial and complex. Aetiopathogenetic factors that have been suggested are: the oncogenic effects of chemotherapy and radiation therapy [29], splenectomy perhaps by altering the immune status of patients with HD and thus contributing to the development of SMN, immunodeficiency either induced by therapy or related to HD [30], and the Epstein-Barr virus (EBV), which seems to play an integral role in the pathogenesis of either de novo NHL [31] or secondary NHL developed after treatment for HD [32].

It is well recognized that the emergence of an abnormal lymphoid proliferation can occur during the impaired immunocompetence in HD patients, in allograft recipients receiving exogenous immunosuppressants, in HIV-positive patients, and in other patients immunocompromised for several reasons [33,34]. The NHLs that have developed in such patients have had the features of high-grade histologic type [1], extranodal location, and a rapid downhill clinical course [35]. Secondary peripheral T-cell lymphoma in our patient was also of high-grade histology and extranodally localized in the lung parenchyme. It appeared after a protracted period of neutropenia and progressive disturbances of humoral and cellular immunity, which resulted from aggressive therapy. It seems more likely that the development of the peripheral T-cell lymphoma of the lungs was connected with the severe and prolonged immunodeficiency that followed the initial therapy.

Recently, the Epstein Barr Virus genome has been shown to be present in the cells of peripheral T-cell lymphoma [36,37] of T-cell lethal-midline granuloma and

angiocentric immunoproliferative lesions (AIL) [38]. In our case we did not have the opportunity to search for either the presence of latent membrane protein (LMP) or the genome of EBV in the HD and AIL involved tissues. Nevertheless, considering the strong association of EBV with HD and AIL, we cannot exclude the possibility (despite the negative serologic results for an EBV infection) that EBV, in the setting of our patient's severe immunodeficiency, played a role at least in the pathogenesis of AIL.

In conclusion, the development of two SMNs in a child with HD within 28 months of the initial diagnosis is a rather rare occurrence. We believe that the development of MDS was related to the initial intensive treatment and its evolution to ANLL, especially since the appearance of monosomy 7 in the abnormal BM clone was rather expected. The development of the peripheral T-cell lymphoma of the AIL type of the lungs in the setting of a nodular sclerosing HD is considered as representing a second malignancy possibly related to the severe immunosuppression of the patient.

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